Parkinsonism and Related Disorders 60 (2019) 14–24

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review article

Pharmacological treatment of apathy in Lewy body disorders: A systematic review

Jennifer Liu[a], Christine A. Cooper[b], Daniel Weintraub[a,c], Nabila Dahodwala[a,*]

[a] Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA
[b] Department of Neurology, Medical University of South Carolina, Charleston, PA, USA
[c] Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

ARTICLE INFO

Keywords:
Apathy
Parkinson's disease
Dementia with Lewy bodies
Movement disorders
Non-motor symptoms
Psychiatric symptoms

ABSTRACT

Introduction: There are no approved treatments for apathy, a frequent and incapacitating symptom in Parkinson's disease (PD) and dementia with Lewy bodies (DLB). We reviewed the literature on the pharmacological treatment of apathy in PD and DLB to inform practice and future research.

Method: We searched PubMed and PsycINFO using the terms "apathy", "treatment", and "Parkinson" or "Lewy body (bodies)." The results were filtered for "clinical trials" and "case reports." We included articles if apathy was measured as an outcome measure, before and after treatment. References of included articles were also reviewed.

Results: The PD search identified 19 articles: 13 randomized control trials (RCTs), 4 open-label studies, 1 case series, and 1 case report. Apathy was the primary outcome in 11 out of 19 studies. A decrease in apathy ratings was seen in 14 of the 19 studies. Of these 14 studies, 9 investigated medications with some dopaminergic effect. Three investigated acetylcholinesterase inhibitors (AChEIs) and found benefit in improving apathy. The DLB search identified 4 articles: 1 RCT, 2 open-label studies, and 1 case series. All 4 studies demonstrated decreased apathy and investigated AChEIs.

Conclusions: We identified 23 studies that assessed the pharmacological treatment of apathy. In PD, agents with dopaminergic activity were the most studied and appeared to have the most benefit. AChEIs also appeared to have benefit in both PD and DLB but were less studied. Future studies of apathy treatment would benefit from larger samples and standardized assessments of apathy to define study populations and endpoints.

1. Introduction

Marin initially described apathy as an amotivational state [1]. More recently, researchers have conceptualized apathy as a result of decreased voluntary action or goal-directed behavior [2]; a multi-dimensional syndrome characterized by impairments in motivation, planning and initiation. Individuals with Parkinson's disease (PD) and dementia with Lewy bodies (DLB), collectively called Lewy body disorders (LBD), often demonstrate some degree of apathy [3]. In PD, apathy may be found in the presence or absence of the common comorbidities of depression, dementia, or fatigue (i.e., overlapping but distinct). In particular, apathy in the absence of depression or dementia has ignited a growing body of literature exploring apathy as an independent construct within LBD [4]. A 2018 international study of 3206 patients with PD demonstrated that apathy was one of the four most important determinants of health-related quality of life [5].

Previous studies have estimated the prevalence of apathy in PD to range from 17% to 70% [6–9], with the variability attributed to different samples and methods of assessing apathy. Apathy rates are higher when there is comorbid depression or cognitive impairment [6,9]. In particular, a high level of apathy is associated with executive dysfunction [10] and decreased gray matter volume in several regions of the frontal lobes [11]. Recent studies have also found that apathy is correlated with greater impairment in patients' activities of daily living and higher caregiver burden [12,13]. The prevalence of apathy in DLB is even higher, with estimates ranging from 35% to up to 100% [14–17].

To date, there are no proven treatments for apathy in LBD, either pharmacological or behavioral. In 2009, Drijgers and colleagues [18] reviewed 35 studies that assessed the pharmacological treatment of apathy in neurodegenerative diseases, of which 3 studies investigated PD and 3 studies investigated DLB. They concluded that there was

* Corresponding author. Penn Neurological Institute, 330 S. 9th Street, Philadelphia, PA, 19107, USA.
E-mail address: Nabila.Dahodwala@uphs.upenn.edu (N. Dahodwala).

https://doi.org/10.1016/j.parkreldis.2018.11.002
Received 19 July 2018; Received in revised form 19 September 2018; Accepted 3 November 2018

insufficient evidence that interventions improve apathy neither in any specific disorder nor across neurodegenerative diseases in general. In 2016, Harrison and colleagues [19] reviewed studies on the treatment of apathy in dementia published from 2013 to 2016 and concluded that acetylcholinesterase inhibitors (AChEIs) and antidepressants did not improve apathy. Given the high prevalence of apathy in LBD, its negative consequences and continued lack of proven therapy, we aimed to systematically review the updated literature on the pharmacological treatment of apathy in LBD in order to better inform clinical practice and future research directions.

2. Method

2.1. Search strategy

Two databases, PubMed and PsycINFO, were searched for articles published until July 1, 2017. The following combined search terms were chosen: “apathy”, “treatment”, and “Parkinson”. The results were filtered for “humans” and “English”, as well as for “clinical trials” and “case reports” separately. A second search of the same two databases was performed with the combined search terms: “apathy”, “treatment”, and “Lewy body (bodies)“. The same filters were applied as in the first search.

2.2. Selection criteria

For each search, the abstracts of the retrieved articles were considered for inclusion if apathy was a primary or secondary outcome measure in a population of patients with LBD. The articles were read in full and included only if they measured apathy before and after pharmacological treatment. Studies testing non-pharmacological interventions, such as non-invasive brain stimulation, surgery, or behavioral therapy, were excluded. There were no limits on the study design, and therefore the selected articles include randomized controlled trials (RCTs), open-label studies, case series, and case reports. Additional articles were identified for inclusion by reviewing the references of the retrieved articles and by checking the Cochrane Library. Any reference whose title suggested that the study might meet our inclusion criteria was identified and subsequently reviewed. Studies identified from references and from the Cochrane Library were subjected to the same inclusion and exclusion criteria as the initial search results.

2.3. Article review

The following data were abstracted from the selected articles: 1) study design and intervention; 2) sample size; 3) apathy as primary or secondary outcome; 4) the scale used to measure apathy; 5) co-occurrence of depression and/or dementia; and 6) main findings. The risk of bias was assessed using the Cochrane Collaboration’s tool for bias risk assessment (Table 1) [20].

3. Results

3.1. Literature search

Overall, a total of 19 articles were found to meet our criteria for the apathy in PD treatment search: 13 RCTs, four open-label studies, one case series, and one case report (Fig. 1). The PubMed search for clinical trials resulted in 28 search items: 12 met final inclusion criteria and 16 were eliminated (investigated effects of deep brain stimulation (9), non-invasive brain stimulation (1), non-pharmacological treatments such as dance and exercise, cognitive training program (3), and did not contain a quantifiable apathy measure (3)). The PubMed search for case reports resulted in seven search items. Of these, none met final inclusion criteria and seven were eliminated (investigated the effects of deep brain stimulation (3), studied a different patient population (3), and did not contain a quantifiable apathy measure (1)).

The PsycINFO search for clinical trials resulted in seven search items: four met final inclusion criteria, all of which were duplicates of the PubMed search results, and three were eliminated (investigated non-invasive brain stimulation (1), did not contain a quantifiable apathy measure (1), and did not measure apathy before and after treatment (1)). The PsycINFO search for case reports resulted in six search items: two met final inclusion criteria and four were eliminated (investigated the effects of deep brain stimulation (2), and studied a different population (2)). After reviewing the references of the included articles and searching the Cochrane Library, five additional articles were identified that met final inclusion criteria for apathy treatment in PD: three RCTs and two open-label studies.

A total of four articles were found to meet our criteria for the second search, apathy treatment in DLB: one RCT, two open-label studies, and one case series (Fig. 2). The PubMed search for clinical trials resulted in three search items, two of which met final inclusion criteria. One was eliminated that did not investigate a pharmacological treatment. The PubMed search for case reports did not result in any search items.

The PsycINFO search for clinical trials resulted in two search items. One met final inclusion criteria but was a duplicate of a PubMed result. The other was eliminated because it did not contain a quantifiable apathy measure. The PsycINFO search for case reports resulted in one search item that was eliminated because it did not contain a quantifiable apathy measure. After reviewing the references of the included articles and searching the Cochrane Library, two additional articles were identified that met final inclusion criteria for apathy treatment in DLB: one RCT and one case series.

3.2. Measurement of apathy (Table 2)

In the 19 PD studies, there were five different scales used to measure apathy, with the exception of an RCT published in 1961, which used a clinical interview to assess apathy [21]. The mostly frequently used scale was the Apathy Scale (AS) [10], which was used in eight out of 19 studies. The Non-Motor Symptoms Scale (NMSS) was used in four studies, and the Neuropsychiatric Inventory (NPI) was used in three studies. Other scales used were the Lille Apathy Rating Scale (LARS) and the Unified Parkinson's Disease Rating Scale (UDPRS). In all four DLB studies, the NPI apathy item was used to measure apathy.

3.3. Main findings: PD (Table 3)

Thirteen double-blind, placebo-controlled RCTs evaluated the effects of treatment of apathy in PD patients, and apathy was the primary outcome in five of these RCTs. Overall, nine out of 13 RCTs demonstrated an improvement in apathy with treatment [21–28]. Breaking down the RCTs by study drug class, the dopamine agonist rotigotine improved apathy in all four RCTs [22–25]. Chaudhuri and colleagues [25] reported in a post-hoc analysis of 267 patients from the RECOVER trial that patients who were treated with rotigotine had a decrease in three out of four apathy items on the mood/apathy domain of the NMSS compared to the control group (item 7: -0.82, 95% CI [-1.18, −0.46]; item 8: -1.11, 95% CI [-1.56, −0.66]; item 12–0.51, 95% CI [-0.96, −0.06]). Antonini and colleagues [22] found that rotigotine decreased scores on one out of four apathy items on the NMSS mood/apathy domain by (item 7: -0.47, 95% CI [-0.91, 0.03]).

Chung and colleagues [23] reported that rotigotine reduced AS scores by 1.27 points, (95% CI [-2.46, −0.07]) compared to placebo. In a study of 116 patients, Hauser and colleagues [25] found that low-dose rotigotine reduced scores on the apathy items on the NMSS mood/apathy domain by 3.14 points (95% CI [-5.76, −0.51]) points compared to placebo. For high-dose rotigotine, there was a 3.09 point decrease (95% CI [-5.58, −0.60]) compared to placebo. However, there was no reduction in AS score for either the high-dose or low-dose group.

Thobois and colleagues [26] found that piribedil, a D_2 and D_3

Table 1
Assessment of risk of bias.

	Author	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
		Randomization	*Allocation concealment*					
1	Chaudhuri et al.	Low	Low	Low	Low	Low	High	Post hoc analysis
2	Antonini et al.	Low	Low	Low	Low	Low	Low	
3	Chung et al.	Low	Low	Low	Low	Low	Low	
4	Hauser et al.	Low	Low	Low	Low	Low	Low	
5	Thobois et al.	Low	Low	Low	Low	Low	Low	
6	Halliday	Unclear	Low	Low	Low	Low	Unclear	Outcomes were assessed through a clinical interview only (study was conducted in 1961)
7	Moreau et al.	Low	Low	Low	Low	Low	Low	
8	Devos et al.	Low	Low	Low	Low	Low	Low	
9	Barone et al.	Low	Low	Low	Low	Low	Low	
10	Smith et al.	Unclear	Unclear	Unclear	Unclear	High	High	Post hoc analysis
11	Weintraub et al.	Unclear	Low	Low	Low	Low	Low	
12	Ory-Magne et al.	Low	Low	Low	Low	Low	Low	
13	Pomponi et al.	Low	Unclear	Low	Low	Low	Low	
14	McKeith et al.	Low	Low	Low	Low	High	Low	
15	Kim et al.	N/A	N/A	High	High	High	Low	Open-label study
16	Litvineko et al.	Unclear	High	High	High	Low	Low	Open-label study
17	Oh et al.	N/A	N/A	High	High	Unclear	Low	Open-label study
18	Hatano et al.	N/A	N/A	High	High	High	High	Open-label study No control group
19	McKeith et al.	N/A	N/A	High	High	Low	High	Open-label study No control group
20	Kimura et al.	N/A	N/A	High	High	Low	Low	Open-label study No control group
21	Solla et al.	N/A	N/A	High	High	Low	High	Case series
22	Chatterjee & Fahn	N/A	N/A	High	High	Low	High	Case report
23	Lanctôt & Herrmann	N/A	N/A	High	High	Low	High	Case series

receptor agonist with a_2-adrenergic antagonist properties, reduced AS scores by 7.3 points, compared to a 0.6 point reduction for placebo, 95% CI not reported, in 37 PD patients post deep brain stimulation surgery without preoperative apathy who became apathetic after discontinuing dopamine agonist therapy postoperatively. Halliday [21] and Moreau and colleagues [29] both studied methylphenidate, primarily a dopamine and norepinephrine reuptake inhibitor. The former found that six out of 10 patients treated with methylphenidate "felt better" on the drug. Of note, this was the only double-blind, placebo-controlled RCT where apathy was assessed through a clinical interview. The latter found that methylphenidate reduced LARS score by seven points, compared to one point reduction for placebo, in 12 patients who were apathetic at baseline, 95% CI not reported.

One group studied acetylcholinesterase inhibitors (AChEIs). Devos and colleagues [27] found in a study of 30 patients that those who were treated with rivastigmine had an 8.5 point reduction in LARS compared a 0.2 point reduction in those treated with placebo, 95% CI not reported.

Aside from double-blind, placebo-controlled RCTs that studied dopaminergic agents and AChEIs, there were five other RCTs that assessed the pharmacologic treatment of apathy in PD. Barone and colleagues [30] did not find that the MAO-B inhibitor rasagiline improved AS scores in 123 patients, although the study was designed to investigate the effect of rasagiline on depressive symptoms. Smith and colleagues [31] did not find that rasagiline improved UDPRS part I apathy item score compared to placebo in 191 patients who were also taking antidepressant medications. Weintraub and colleagues [32] did not find atomoxetine, a selective norepinephrine reuptake inhibitor, to improve AS scores in 55 patients. Ory-Magne and colleagues [28] studied amantadine, an agonist at many different neurotransmitter receptors (including dopamine, norepinephrine, and serotonin), and found a decrease in AS scores by 0.9 points (95% CI [-1.9, 0.1]), compared to a 0.7 point increase for placebo, per caregiver report but not per patient report in 56 patients. Pomponi and colleagues [33] found no difference between docosahexaenoic acid (DHA), an omega-3 fatty acid, and placebo in improving AS scores in 24 patients.

Four open-label studies assessed the treatment of apathy in PD patients, all of which evaluated apathy as a primary outcome. Notably, only one out of the four studies included a control group. Overall, three out of four open-label studies showed an improvement in apathy with treatment [34–36]. One study investigated dopaminergic medications. Kim and colleagues [36] studied 16 de novo PD patients and found that dopaminergic medications (converted to a levodopa equivalent daily dose) did not improve scores on the apathy items on the NMSS mood/apathy domain.

Two open-label studies investigated AChEIs. In an open controlled trial, Litvineko and colleagues [34] found that galantamine decreased NPI apathy symptom severity scores by 1.4 points in 41 patients, 95% CI and NPI apathy item scores for the control group were not reported. In a study of 23 patients, Oh and colleagues [37] found that the rivastigmine did not decrease NPI apathy symptom severity scores, although there was a 0.7 point decrease in caregiver distress, 95% CI not reported. Of note, this study did not include a control group. Hatano and colleagues [35] investigated yokukansan, a traditional Japanese medicine, and found it to significantly improve NPI apathy scores in 23 patients, exact scores not reported. This study also did not include a control group.

Two case reports investigated the treatment of apathy in PD patients, both of which evaluated apathy as a primary outcome. Solla and colleagues [38] found that there was a worsening of AS score with tapering dopamine agonists in the setting of initiating levodopa-carbidopa intestinal gel infusion. Chatterjee and Fahn [39] reported a three point decrease in UDPRS item four with methylphenidate in a patient whose depression was successfully treated prior to initiating methylphenidate.

Table 2
Overview of apathy rating scales utilized.

Name of scale	Number of items	Range of scores[a]	Domains measured	Informant (patient, caregiver, clinician)	Movement Disorder Society classification (Recommended, Suggested, Listed)	# of studies using scale
NMSS items 7, 8, 11, 12	4	0 to 48	Motivation	Patient, caregiver, clinician	Not assessed	4
AS	14	0 to 42	Motivation, mood	Patient, caregiver	Recommended for assessing severity	8
LARS	33	− 36 to 36	Intellectual curiosity, self-awareness, mood and initiation	Patient, caregiver	Recommended for assessing severity	2
NPI item 7	3[b]	Patient symptom severity: 1 to 3; caregiver distress: 0 to 5	Motivation	Caregiver	Suggested for screening and assessing severity	7
UPDRS item 4	1	0 to 4	Motivation	Patient, caregiver, clinician	Recommended for screening	1
Clinical interview			– Not applicable –			1

AS: Apathy Scale; **LARS:** Lille Apathy Rating Scale; **NMSS:** Non-Motor Symptoms Scale; **NPI:** Neuropsychiatric Inventory; **UPDRS:** Unified Parkinson's Disease Rating Scale.

[a] Higher scores indicate greater apathy.

[b] One screening question, if positive then two additional questions.

3.4. Main findings: DLB (Table 4)

Only one RCT assessed the treatment of apathy in DLB patients. Notably, apathy was a primary outcome measure in this RCT. McKeith and colleagues [40] found that there was an improvement in NPI apathy score after treatment with rivastigmine in 120 patients, although exact values were not reported.

Two open-label studies evaluated the treatment of apathy in DLB, neither of which included a control group. After the above RCT concluded and a drug-free interval elapsed, McKeith and colleagues [41] continued to investigate rivastigmine in a small proportion of the same group of patients (11 out of 120) using an open-label study and found that there was a 63% reduction in the NPI apathy score with rivastigmine, although exact values were not provided. Kimura and colleagues [42] found that ferulic acid and *Angelica archangelica* extract reduced NPI apathy scores by 3.3 points in a study of ten patients, 95% CI not reported.

One case series assessed the treatment of apathy in DLB patients and evaluated apathy as a primary outcome. Lanctôt & Herrmann [43] reported that in a series of seven patients of whom four were apathetic, all four patients had a decrease in the NPI apathy score to zero after receiving the AChEI donepezil.

4. Discussion

We present a systematic review of the pharmacological treatment of apathy with a specific focus on the LBD population. Previous reviews of the treatment of apathy across many types of dementia and neurodegenerative disorders reported insufficient evidence that apathy improves with drug therapy [18,19]. In this review, 14 out of 19 PD studies and all 4 DLB studies found that treatment improved apathy, although there are several important points for further discussion.

In the PD population, agents with dopaminergic activity were the most studied. Of the 14 studies that showed a decrease in apathy with pharmacologic treatment, 9 assessed an agent with some dopaminergic activity. Seven of these dopaminergic agent studies were RCTs; however, only three RCTs assessed a dopaminergic agent in a study design with apathy as a primary outcome [21,25,26]. Moreover, in one of the RCTs, apathy was assessed through a clinical interview as the study was conducted in 1961, before the current scales to measure apathy were available [21]. Therefore, although dopaminergic agents may be a promising treatment for apathy in PD, still lacking are high-quality RCTs that focus primarily on apathy.

Consistent with previous studies in dementia that demonstrated an improvement in apathy with AChEIs [44], in this review there appears to be evidence for the role of AChEIs in the treatment of apathy in PD, although the number of studies was limited. Three out of three studies found an improvement in apathy with AChEIs, but only one was an RCT [27]. Apart from dopaminergic agents and AChEIs, one RCT found evidence that amantadine was effective and one open-label study found that the traditional Japanese herbal medicine yokukansan showed effectiveness. For herbal medicines, it is not possible to draw firm conclusions about their role in the treatment of apathy in PD due to several limitations including small number of studies, small sample sizes, and lack of a placebo condition.

Although apathy is seen more commonly in DLB [45], we identified only four studies that evaluated pharmacological treatment. There were three studies that evaluated AChEIs, of which one was a double-blind, placebo-controlled RCT with apathy as a primary outcome and found evidence for the benefit of rivastigmine. Given the limited number of studies, the role of medications in the treatment of apathy in DLB remains unclear.

Researchers have suggested that treatment of apathy may benefit from investigating the individual subdomains of apathy separately [46]. Apathy has been conceptualized by Levy and Dubois as a deficit of goal-directed behavior in any of 3 subdomains: emotional-affective

Table 3
Summary of reviewed articles for treatment of apathy in Parkinson's disease.

Study	Drug	Total N	1° vs. 2° outcome	Scale	Exclusions for depression and dementia?	Results	Comments
Double-blind randomized controlled trials, placebo-controlled							
Chaudhuri et al. (2013)	Rotigotine	267	2	NMSS	Not part of inclusion or exclusion criteria	−0.82 points on NMSS question 7, 95% CI (−1.18, −0.46), $p < 0.0001$ −1.11 points on NMSS question 8, 95% CI (−1.56, 0.66), $p < 0.0001$ −0.51 points on NMSS question 12, 95% CI (−0.96, −0.06), $p = 0.026$ No significant difference on NMSS question 11	
Antonini et al. (2015)	Rotigotine	447	2	NMSS	Not part of inclusion or exclusion criteria	−0.47 points on NMSS question 8, 95% CI (−0.91, 0.03), $p = 0.036$ No significant difference on NMSS question 7, 11, 12	
Chung et al. (2016)	Rotigotine	364	2	AS	Depression was an inclusion criterion Dementia excluded	−1.27 points on AS, 95% CI (−2.46, −0.07), $p = 0.0378$	32 discontinued in placebo group (16 due to adverse events) 35 discontinued in rotigotine group (25 due to adverse events) Anhedonia was evaluated using SHAPS (secondary), there was no significant difference in SHAPS score ($p = 0.4717$)
Hauser et al. (2016)	Rotigotine	116	1 and 2	AS (1°) NMSS (2°)	Severe depression (BDI ≥29) excluded Dementia excluded	No significant difference on AS Low-dose rotigotine: -3.14 points on apathy items in NMSS mood/apathy domain, 95% CI (−5.76, −0.51), $p = 0.0196$ High-dose rotigotine: -3.09 points on apathy items in NMSS mood/apathy domain, 95% CI (−5.58, −0.60), $p = 0.0156$	
Thobois et al. (2013)	Piribedil	37	1	AS	Yes	−7.3 points on AS, $p = 0.015$	Study population was patients who became apathetic as a result of STN DBS Patients with preoperative apathy were excluded
Halliday (1961)	Methylphenidate	10	1	Clinical interview	Not part of inclusion or exclusion criteria	6 out of 10 patients “felt better” on the drug	Crossover study Apathy was assessed by clinical interview
Moreau et al. (2012)	Methylphenidate	69	2	LARS	Yes	−7 points on LARS, $p = 0.03$	
Devos et al. (2014)	Rivastigmine	30	1	LARS	Yes	−8.5 points on LARS, $p = 0.034$	Improved caregiver burden and ADLs, not patient quality of life
Barone et al. (2015)	Rasagiline	123	2	AS	Depression was an inclusion criterion Dementia excluded as part of inclusion criteria	No significant difference	
Smith et al. (2015)	Combined rasagiline and antidepressant	191	2	MDS-UDPRS	Major depression (clinical diagnosis) excluded Dementia not assessed	No significant difference	No concomitant antiparkinsonian medication was permitted Permitted antidepressants: amitriptyline, trazodone, citalopram, sertraline, paroxetine, escitalopram
Weintraub et al. (2010)	Atomoxetine	55	2	AS	Depression was an inclusion criterion Dementia excluded	No significant difference	Study population was PD patients with depression

(*continued on next page*)

Table 3 (*continued*)

Study	Drug	Total N	1° vs. 2° outcome	Scale	Exclusions for depression and dementia?	Results	Comments
Ory-Magne et al. (2014)	Amantadine	56	2	AS	Yes	−0.9 point on AS, 95% CI (−1.9, 0.1), p = 0.04 per caregiver report No significant difference per patient report	Dyskinesias also increased off amantadine, may have confounded caregiver's impression of apathy
Pomponi et al. (2014)	DHA	24	1	AS	Depression was an inclusion criterion Dementia excluded	No significant difference	
Open-label studies							
Kim et al. (2009)	Dopaminergic medications	16	1	NMSS	Depression not assessed Dementia excluded	No significant difference on NMSS questions 7, 8, 11, 12	De novo PD patients, no control group
Litvinenko et al. (2008)	Galantamine	41	1	NPI	Marked depression (Hamilton Depression Scale score > 18) excluded Dementia was an inclusion criterion	−1.4 points on NPI item 7 at 12 weeks ($p < 0.05$) and 25 weeks ($p < 0.01$)	Open controlled trial
Oh et al. (2015)	Rivastigmine	23	1	NPI	Depression was excluded Dementia was an inclusion criterion	No significant difference on NPI item 7 for symptom severity −0.7 point on NPI item 7 for caregiver distress, p = 0.009	No control group
Hatano et al. (2014)	Yokukansan	23	1	NPI	Depression was not part of the inclusion or exclusion criteria Dementia excluded	Decrease on NPI item 7 ($p < 0.05$). Results were shown graphically but exact values were not reported	No control group
Case series and case reports							
Solla et al. (2015)	LCIG	4	1	AS	Yes	Increase in AS score when tapering dopamine agonists in the setting of initiation LCIG	
Chatterjee & Fahn (2002)	Methylphenidate	1	1	UPDRS	Depression successfully treated prior to methylphenidate trial Dementia excluded	−3 points on UDPRS item 4 (motivation/initiative)	

ADL: Activities of daily living; **AS:** Apathy Scale; **BDI**: Beck Depression Inventory; **DHA:** docosahexaenoic acid; **LARS:** Lille Apathy Rating Scale; **LCIG:** levodopa-carbidopa intestinal gel; **MAO-B:** monoamine oxidase B; **MDS-UPDRS:** Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; **MMSE:** Mini-Mental State Examination; **NMSS:** Non-Motor Symptoms Scale; **NPI:** Neuropsychiatric Inventory; **PD:** Parkinson's disease; **SHAPS:** Snaith-Hamilton Pleasure Scale; **STN-DBS:** deep brain stimulation of the subthalamic nucleus; **UPDRS:** United Parkinson's Disease Rating Scale.

Table 4
Summary of reviewed articles for the treatment of apathy in Dementia with Lewy bodies.

Study	Drug	Total N	Apathy as 1° vs. 2° Outcome	Scale	Exclusions for depression?	Results	Comments
Double-blind randomized controlled trials, placebo-controlled							
McKeith et al. (2000)	Rivastigmine	120	1	NPI	Depression not part of inclusion or exclusion criteria Patients with MMSE < 10 excluded	Decrease in NPI item 7 score. Exact values not reported	
Open-label studies							
McKeith et al. (2000)[a]	Rivastigmine	11	2	NPI	Depression not part of inclusion or exclusion criteria Patients with MMSE < 10 excluded	Decrease in NPI item 7 score by 63%. Exact values not reported	No control group
Kimura et al. (2011)	Ferulic acid	10	1	NPI	Depression and prior antidepressant use excluded Dementia was an inclusion criterion	− 3.3 points on NPI item 7, $p < 0.02$	No control group
Case series							
Lanctôt & Herrmann (2000)	Donepezil	7	1	NPI	Not part of inclusion or exclusion criteria	All patients with apathy (4 of 7) had a resolution of apathy (NPI item 7 score decreased to 0)	

MMSE: Mini-Mental Status Examination; **NPI:** Neuropsychiatric Inventory.
[a] after 20 weeks of double-blind treatment and 3 weeks of drug free-time, a small proportion of patients from the RCT continued to receive rivastigmine in an open-label study.

(motivation), cognitive (planning), or auto-activation (initiation) [2]. The authors also proposed the underlying neuroanatomy of these subdomains based on clinical observations of apathetic patients with lesions of the prefontal cortex (PFC) and basal ganglia: emotional-affective was mapped to the orbitomedial PFC and ventral striatum; cognitive to the lateral PFC and dorsal caudate nuclei; and auto-activation to the bilateral internal portions of the globus pallidus, bilateral paramedian thalami, and the dorsomedial PFC.

All subdomains of apathy appear to be involved in PD, but the extent to which each subdomain is implicated has not been quantified. Czernecki and colleagues [47] found that PD patients had a decrease in apathy in the "on" state with levodopa therapy compared to the "off" state, suggesting that apathy in this population is in part dopamine-mediated. Though PD is characterized by a deficit in dopamine, a neurotransmitter widely involved in reward processing [48], it is insufficient to say that apathy in PD is predominantly emotional-affective because apathy is prevalent early in the course of PD when the dopaminergic mesocorticolimbic pathway is relatively spared [49]. Furthermore, Tremblay and colleagues [50] found in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-lesioned monkeys, an animal model of PD, that apathy also occurs when signaling within the dorsolateral PFC and dorsal caudate nuclei is impaired, suggesting that apathy in PD is in part mitigated by non-motor, non-dopaminergic pathways as well. Finally, PD patients have more difficulty compared to those without PD with spontaneous activation of mental processes or actions (i.e., auto-activation) in the absence of external stimuli [51].

Pagonabarraga and colleagues proposed that determining the predominant subdomain of apathy in PD patients may help guide the choice of therapy: dopamine agonists and other dopaminergic drugs, such as methylphenidate, for emotional-affective deficits; AChEIs for cognitive deficits; and dopamine agonists for auto-activation deficits [46]. In our review, the PD studies that included patients with dementia [34,37] and all but one of the DLB studies investigated the use of AChEIs. On the other hand, drugs with dopaminergic activity increase the availability of dopamine to act on the neurocircuitry that underlies two of three apathy subdomains (i.e., emotional-affective, auto-activation), which may explain why dopaminergic agents were the most studied medications for apathy in PD. In the future, it will be especially important for studies investigating neurotherapeutics with less well known mechanisms of action (e.g., *Angelica archangelica*, ferulic acid, omega-3 fatty acids, yokukansan) to describe their drug of choice in context of the proposed mechanisms of apathy.

Given the high comorbidity of depression with apathy, it is important to optimize the treatment of depressive symptoms in apathetic patients with LBD. While selective serotonin reuptake inhibitors (SSRIs) are often used to treat depression, there is evidence that SSRI use may be associated with greater apathy [19,52]. One study that showed an association between SSRI use and worsened apathy in PD also found that non-SSRI antidepressants were not associated with apathy [52]. Although the etiology of the association between SSRIs and apathy is not known, it is interesting to note in our review that nine out of 10 PD studies (90%) that excluded depression demonstrated an improvement in apathy, while only five out of nine PD studies (55.6%) that did not exclude depression, and therefore may have enrolled patients on SSRIs, showed improvement. Moreover, apathy is highly comorbid with fatigue, and both are key determinants of health-related quality of life in PD that nevertheless have been challenging to assess and lack firm evidence-based guidelines for treatment [5,53,54].

An additional challenge in studying the treatment of apathy in LBD is how to best measure apathy. Formal apathy screening is rarely performed outside the setting of research, thus it is difficult to determine the clinical significance of a change in apathy scale score. In a 2008 critique of the most commonly used apathy scales [55], the widely used UDPRS item 4 was recommended as a screening tool for apathy. As it is only one item that focuses on a single dimension of apathy (motivation), it is not appropriate for assessing symptom severity or response to

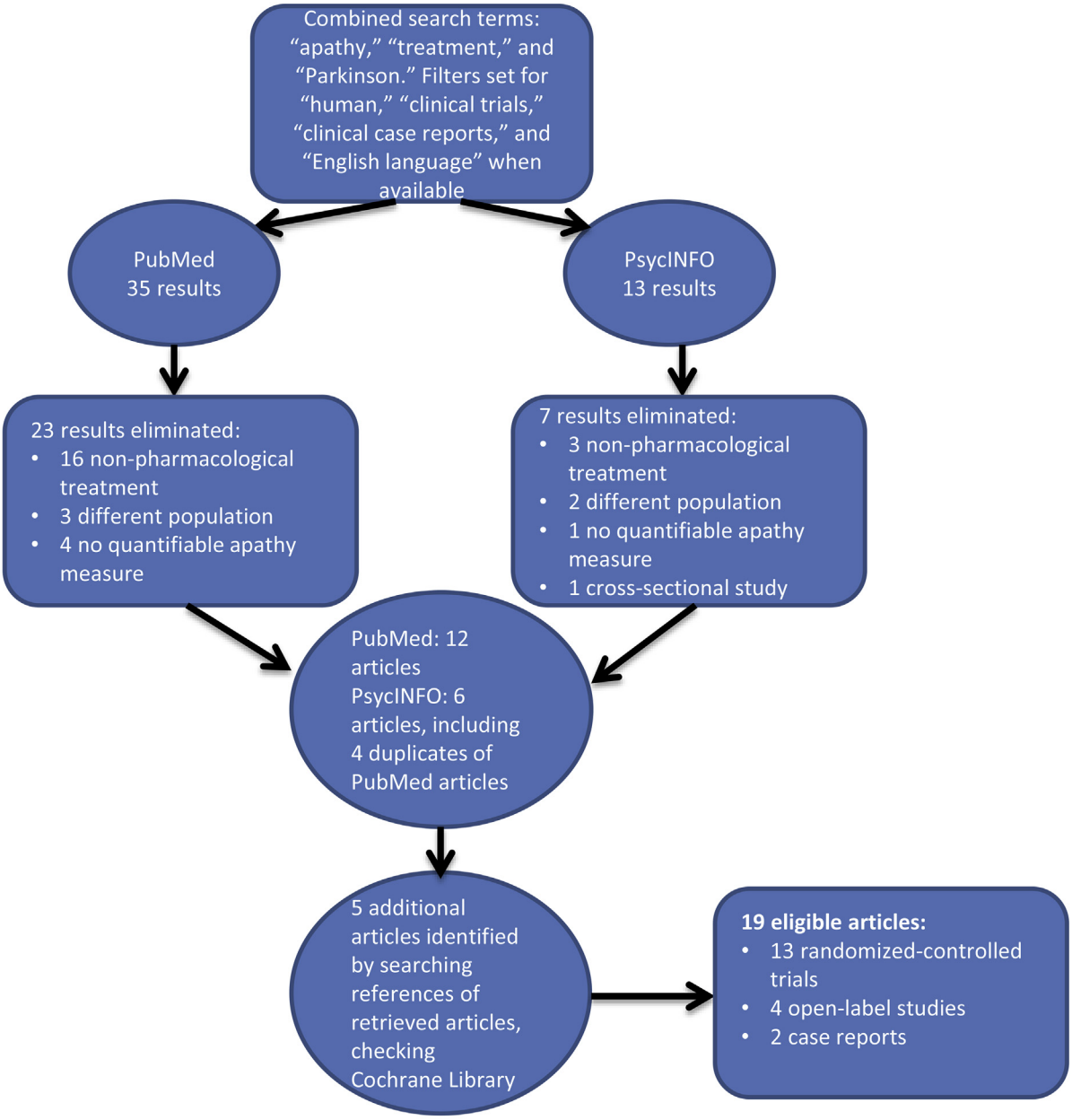

Fig. 1. Literature search and selection of articles investigating apathy treatment in Parkinson's disease.

therapy. The AS was noted for its sensitivity to change and recommended for assessing the severity of apathy in PD. In this critique, the LARS earned a rating of "suggested", but the rating was subsequently updated to "recommended" after sensitivity to change was demonstrated [56,57]. While the AS and the LARS assess multiple domains of apathy, they also include several mood items.

In the same critique, the Apathy Evaluation Scale [58], Apathy Inventory [59, and NPI [60] were unable to be recommended for measuring apathy due to paucity of data on validity (Apathy Evaluation Scale and Apathy Inventory) or clinimetric properties (NPI). The NPI item 7 (apathy item) was given a rating of "suggested" for screening and measuring the severity of apathy, but it also only assesses motivation. To our knowledge, the NMSS, employed by several studies in this review, has not been critiqued on its utility to screen for or measure apathy. Like the UPDRS item 4 and NPI item 7, it only assesses a single subdomain: motivation. Furthermore, apathy scores differ as a function of the informant (e.g, patient, caregiver, or clinician), as demonstrated by several studies in this review that found a decrease in apathy from the caregiver but not from the patient perspective [27,36]. Future research that focuses on objective, multidimensional testing of apathy may address some of the limitations of the existing scales.

This review has several limitations. There are a limited number of high-quality studies that measure apathy as a primary outcome. Most studies included in this review investigated multiple neuropsychiatric symptoms of LBD using scales that contain many domains, of which apathy is only one. Additionally, the studies included in this review may have been affected by publication bias. Studies utilizing scales that contain many domains may prioritize reporting only the overall score and may include the apathy item score only if there is a statistically significant difference. Our search strategy does not capture studies in which a scale containing apathy items was used but an apathy item score was not reported. Finally, there is a paucity of studies that investigate apathy in the DLB population even though the prevalence of apathy may exceed that of the PD population. Future high-quality RCTs

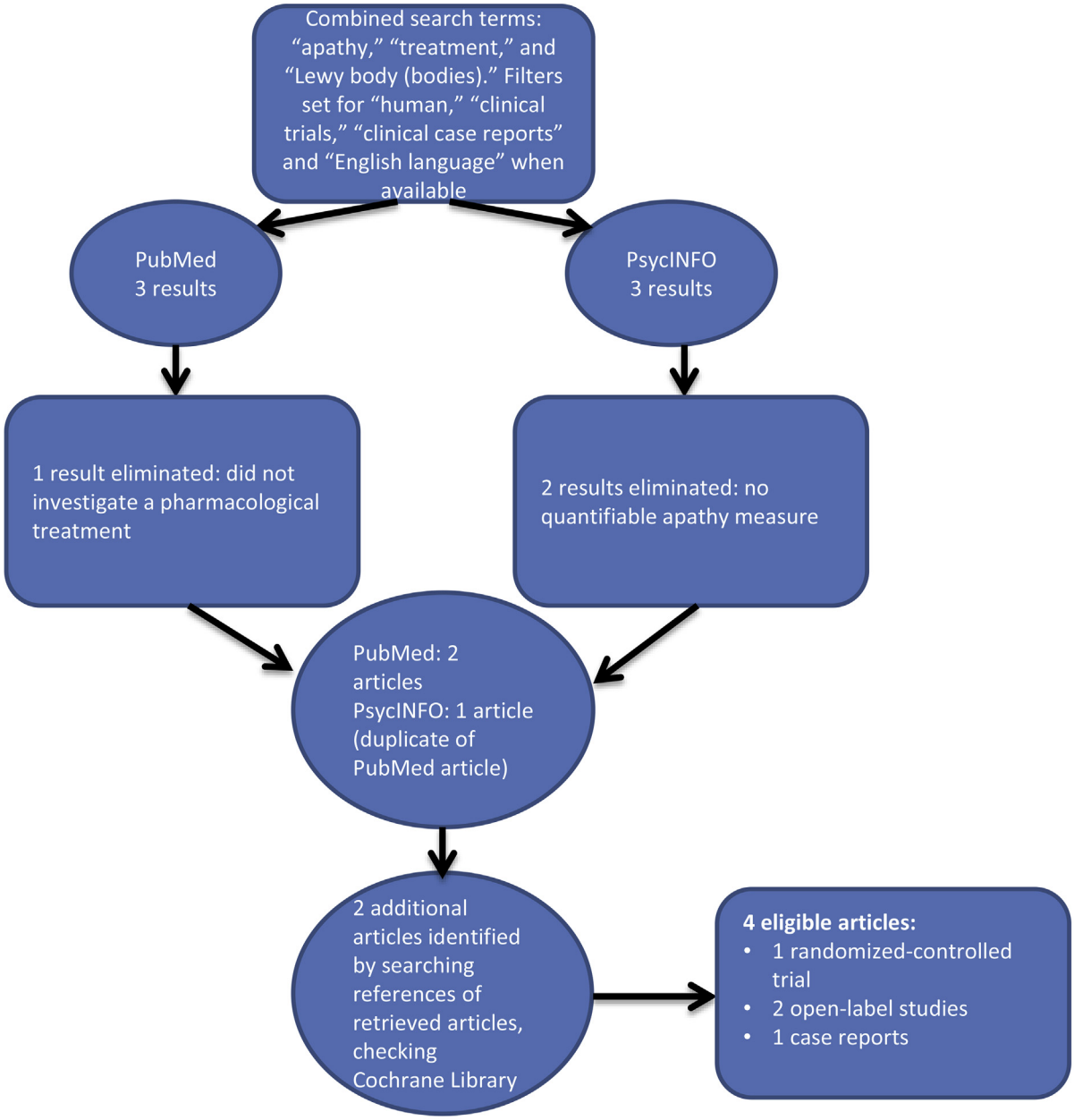

Fig. 2. Literature search and selection of articles investigating apathy treatment in Dementia with Lewy bodies.

that measure apathy as a primary outcome in both PD and DLB populations may clarify the most beneficial agents for the treatment of apathy in these patients.

5. Conclusions

Apathy is prevalent in LBD. It hinders activities of daily living and increases caregiver distress. To date, there is no proven treatment for apathy in these patients. In this systematic review of studies that assessed the pharmacological treatment of apathy in LBD, more than 75% of studies demonstrated an improvement in apathy scores after treatment. In PD, dopaminergic agents were the most studied class and seemed to have the greatest efficacy. AChEIs also appeared to be of benefit, although the number of studies was limited. Data from DLB studies were limited, but suggested that AChEIs may be a promising area of further research. Future studies will benefit from identifying the subdomains of apathy, tailoring the therapy of choice to the corresponding subdomain, and selecting a more sensitive, specific, and objective measure of apathy in which a change in score can reliably be translated into a clinically meaningful change.

Declarations of interest

None.

Acknowledgements

This work was supported by the Parkinson Council and Parkinson Foundation, USA (PDF-TRG-1724).

References

[1] R.S. Marin, Apathy: a neuropsychiatric syndrome, J. Neuropsychiatry Clin. Neurosci. 3 (3) (1991) 243–254.
[2] R. Levy, B. Dubois, Apathy and the functional anatomy of the prefrontal

cortex–basal ganglia circuits, Cerebr. Cortex 16 (7) (2006) 916–928.
[3] S.E. Starkstein, Apathy in Parkinson's disease: diagnostic and etiological dilemmas, Mov. Disord.: Off. J. Mov. Disord. Soc. 27 (2) (2012) 174–178, https://doi.org/10.1002/mds.24061.
[4] S.E. Starkstein, A.F. Leentjens, The nosological position of apathy in clinical practice, J. Neurol. Neurosurg. Psychiatry 79 (10) (2008) 1088–1092, https://doi.org/10.1136/jnnp.2007.136895.
[5] M. Skorvanek, P. Martinez-Martin, N. Kovacs, I. Zezula, M. Rodriguez-Violante, J.C. Corvol, et al., Relationship between the MDS-UPDRS and Quality of Life: a large multicenter study of 3206 patients, Park. Relat. Disord. 52 (2018) 83–89, https://doi.org/10.1016/j.parkreldis.2018.03.027.
[6] K. Dujardin, P. Sockeel, D. Devos, M. Delliaux, P. Krystkowiak, A. Destee, et al., Characteristics of apathy in Parkinson's disease, Mov. Disord.: Off. J. Mov. Disord. Soc. 22 (6) (2007) 778–784, https://doi.org/10.1002/mds.21316.
[7] G.C. Pluck, R.G. Brown, Apathy in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 73 (6) (2002) 636–642.
[8] K.F. Pedersen, J.P. Larsen, G. Alves, D. Aarsland, Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study, Park. Relat. Disord. 15 (4) (2009) 295–299.
[9] D. Aarsland, L. Marsh, A. Schrag, Neuropsychiatric symptoms in Parkinson's disease, Mov. Disord.: Off. J. Mov. Disord. Soc. 24 (15) (2009) 2175–2186, https://doi.org/10.1002/mds.22589.
[10] S.E. Starkstein, H.S. Mayberg, T.J. Preziosi, P. Andrezejewski, R. Leiguarda, R.G. Robinson, Reliability, validity, and clinical correlates of apathy in Parkinson's disease, J. Neuropsychiatry Clin. Neurosci. 4 (2) (1992) 134–139.
[11] S. Martinez-Horta, F. Sampedro, J. Pagonabarraga, R. Fernandez-Bobadilla, J. Marin-Lahoz, J. Riba, et al., Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes, Brain Imag. Behav. 11 (5) (2017) 1334–1342, https://doi.org/10.1007/s11682-016-9607-5.
[12] Leiknes I, Tysnes OB, Aarsland D, Larsen JP. Caregiver distress associated with neuropsychiatric problems in patients with early Parkinson's disease: the Norwegian ParkWest study. Acta Neurol. Scand.. 1111;122(6):418-424.
[13] I. Leroi, V. Harbishettar, M. Andrews, K. McDonald, E.J. Byrne, A. Burns, Carer burden in apathy and impulse control disorders in Parkinson's disease, Int. J. Geriatr. Psychiatr. 27 (2) (2012) 160–166.
[14] S. Engelborghs, K. Maertens, G. Nagels, E. Vloeberghs, P. Marien, A. Symons, et al., Neuropsychiatric symptoms of dementia: cross-sectional analysis from a prospective, longitudinal Belgian study, Int. J. Geriatr. Psychiatr. 20 (11) (2005) 1028–1037, https://doi.org/10.1002/gps.1395.
[15] B. Borroni, M. Turla, V. Bertasi, C. Agosti, N. Gilberti, A. Padovani, Cognitive and behavioral assessment in the early stages of neurodegenerative extrapyramidal syndromes, Arch. Gerontol. Geriatr. 47 (1) (2008) 53–61, https://doi.org/10.1016/j.archger.2007.07.005.
[16] R. Perri, M. Monaco, L. Fadda, C. Caltagirone, G.A. Carlesimo, Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular, and lewy body dementias: a comparative study, J. Alzheim. Dis.: JAD. 39 (3) (2014) 669–677, https://doi.org/10.3233/jad-131337.
[17] G. Amoo, R.O. Akinyemi, L.U. Onofa, J.O. Akinyemi, O. Baiyewu, A.O. Ogunlesi, et al., Profile of clinically-diagnosed dementias in a neuropsychiatric practice in Abeokuta, south-western Nigeria, Afr. J. Psychiatr. 14 (5) (2011) 377–382 https://doi.org/10.4314/ajpsy.v14i5.5.
[18] R.L. Drijgers, P. Aalten, A. Winogrodzka, F.R. Verhey, A.F. Leentjens, Pharmacological treatment of apathy in neurodegenerative diseases: a systematic review, Dement. Geriatr. Cognit. Disord. 28 (1) (2009) 13–22, https://doi.org/10.1159/000228840.
[19] F. Harrison, L. Aerts, H. Brodaty, Apathy in dementia: systematic review of recent evidence on pharmacological treatments, Curr. Psychiatr. Rep. 18 (11) (2016) 103, https://doi.org/10.1007/s11920-016-0737-7.
[20] J.P. Higgins, D.G. Altman, P.C. Gotzsche, P. Juni, D. Moher, A.D. Oxman, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, Br. Med. J. 343 (2011), https://doi.org/10.1136/bmj.d5928 d5928.
[21] A.M. Halliday, P.W. Nathan, Methyl phenidate in parkinsonism, Br. Med. J. 1 (5240) (1961) 1652–1655.
[22] A. Antonini, L. Bauer, E. Dohin, W.H. Oertel, O. Rascol, H. Reichmann, et al., Effects of rotigotine transdermal patch in patients with Parkinson's disease presenting with non-motor symptoms - results of a double-blind, randomized, placebo-controlled trial, Eur. J. Neurol.: Off. J. Eur. Fed. Neurol. Soc. 22 (10) (2015) 1400–1407, https://doi.org/10.1111/ene.12757.
[23] S.J. Chung, M. Asgharnejad, L. Bauer, F. Ramirez, B. Jeon, Evaluation of rotigotine transdermal patch for the treatment of depressive symptoms in patients with Parkinson's disease, Expet Opin. Pharmacother. 17 (11) (2016) 1453–1461, https://doi.org/10.1080/14656566.2016.1202917.
[24] K. Ray Chaudhuri, P. Martinez-Martin, A. Antonini, R.G. Brown, J.H. Friedman, M. Onofrj, et al., Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER, Park. Relat. Disord. 19 (7) (2013) 660–665, https://doi.org/10.1016/j.parkreldis.2013.02.018.
[25] R.A. Hauser, J. Slawek, P. Barone, E. Dohin, E. Surmann, M. Asgharnejad, et al., Evaluation of rotigotine transdermal patch for the treatment of apathy and motor symptoms in Parkinson's disease, BMC Neurol. 16 (2016) 90, https://doi.org/10.1186/s12883-016-0610-7.
[26] S. Thobois, E. Lhommee, H. Klinger, C. Ardouin, E. Schmitt, A. Bichon, et al., Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil, Brain: J. Neurol. 136 (Pt 5) (2013) 1568–1577, https://doi.org/10.1093/brain/awt067.
[27] D. Devos, C. Moreau, D. Maltete, R. Lefaucheur, A. Kreisler, A. Eusebio, et al., Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial, J. Neurol. Neurosurg. Psychiatry 85 (6) (2014) 668–674, https://doi.org/10.1136/jnnp-2013-306439.
[28] F. Ory-Magne, J.C. Corvol, J.P. Azulay, A.M. Bonnet, C. Brefel-Courbon, P. Damier, et al., Withdrawing amantadine in dyskinetic patients with Parkinson disease: the AMANDYSK trial, Neurology 82 (4) (2014) 300–307, https://doi.org/10.1212/wnl.0000000000000050.
[29] C. Moreau, A. Delval, L. Defebvre, K. Dujardin, A. Duhamel, G. Petyt, et al., Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial, Lancet Neurol. 11 (7) (2012) 589–596, https://doi.org/10.1016/s1474-4422(12)70106-0.
[30] P. Barone, G. Santangelo, L. Morgante, M. Onofrj, G. Meco, G. Abbruzzese, et al., A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients, Eur. J. Neurol.: Off. J. Eur. Fed. Neurol. Soc. 22 (8) (2015) 1184–1191, https://doi.org/10.1111/ene.12724.
[31] K.M. Smith, E. Eyal, D. Weintraub, Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability, JAMA Neurol. 72 (1) (2015) 88–95, https://doi.org/10.1001/jamaneurol.2014.2472.
[32] D. Weintraub, S. Mavandadi, E. Mamikonyan, A.D. Siderowf, J.E. Duda, H.I. Hurtig, et al., Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease, Neurology 75 (5) (2010) 448–455, https://doi.org/10.1212/WNL.0b013e3181ebdd79.
[33] M. Pomponi, G. Loria, S. Salvati, A. Di Biase, G. Conte, C. Villella, et al., DHA effects in Parkinson disease depression, Basal Ganglia 4 (2) (2014) 61–66.
[34] I.V. Litvinenko, M.M. Odinak, V.I. Mogil'naya, A.Y. Emelin, Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial), Neurosci. Behav. Physiol. 38 (9) (2008) 937–945, https://doi.org/10.1007/s11055-008-9077-3.
[35] T. Hatano, N. Hattori, T. Kawanabe, Y. Terayama, N. Suzuki, Y. Iwasaki, et al., An exploratory study of the efficacy and safety of yokukansan for neuropsychiatric symptoms in patients with Parkinson's disease, J. Neural. Transm. 121 (3) (2014) 275–281, https://doi.org/10.1007/s00702-013-1105-y (Vienna, Austria : 1996).
[36] H.J. Kim, S.Y. Park, Y.J. Cho, K.S. Hong, J.Y. Cho, S.Y. Seo, et al., Nonmotor symptoms in de novo Parkinson disease before and after dopaminergic treatment, J. Neurol. Sci. 287 (1–2) (2009) 200–204, https://doi.org/10.1016/j.jns.2009.07.026.
[37] Y.S. Oh, J.S. Kim, P.H. Lee, Effect of rivastigmine on behavioral and psychiatric symptoms of Parkinson's disease dementia, J. Mov. Disord. 8 (2) (2015) 98–102, https://doi.org/10.14802/jmd.15041.
[38] P. Solla, A. Fasano, A. Cannas, C.S. Mulas, M.G. Marrosu, A.E. Lang, et al., Dopamine agonist withdrawal syndrome (DAWS) symptoms in Parkinson's disease patients treated with levodopa-carbidopa intestinal gel infusion, Park. Relat. Disord. 21 (8) (2015) 968–971, https://doi.org/10.1016/j.parkreldis.2015.05.018.
[39] A. Chatterjee, S. Fahn, Methylphenidate treats apathy in Parkinson's disease, J. Neuropsychiatry Clin. Neurosci. 14 (4) (2002) 461–462, https://doi.org/10.1176/jnp.14.4.461.
[40] I. McKeith, T. Del Ser, P. Spano, M. Emre, K. Wesnes, R. Anand, et al., Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study, Lancet 356 (9247) (2000) 2031–2036, https://doi.org/10.1016/s0140-6736(00)03399-7.
[41] I.G. McKeith, J.B. Grace, Z. Walker, E.J. Byrne, D. Wilkinson, T. Stevens, et al., Rivastigmine in the treatment of dementia with Lewy bodies: preliminary findings from an open trial, Int. J. Geriatr. Psychiatr. 15 (5) (2000) 387–392.
[42] T. Kimura, H. Hayashida, M. Murata, J. Takamatsu, Effect of ferulic acid and Angelica archangelica extract on behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies, Geriatr. Gerontol. Int. 11 (3) (2011) 309–314, https://doi.org/10.1111/j.1447-0594.2010.00687.x.
[43] K.L. Lanctot, N. Herrmann, Donepezil for behavioural disorders associated with Lewy bodies: a case series, Int. J. Geriatr. Psychiatr. 15 (4) (2000) 338–345.
[44] K. Berman, H. Brodaty, A. Withall, K. Seeher, Pharmacologic treatment of apathy in dementia, Am. J. Geriatr. Psychiatry: Off. J. American Assoc. Geriatr. Psychiatr. 20 (2) (2012) 104–122, https://doi.org/10.1097/JGP.0b013e31822001a6.
[45] T. Del Ser, I. McKeith, R. Anand, A. Cicin-Sain, R. Ferrara, R. Spiegel, Dementia with lewy bodies: findings from an international multicentre study, Int. J. Geriatr. Psychiatr. 15 (11) (2000) 1034–1045.
[46] J. Pagonabarraga, J. Kulisevsky, A.P. Strafella, P. Krack, Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment, Lancet Neurol. 14 (5) (2015) 518–531, https://doi.org/10.1016/s1474-4422(15)00019-8.
[47] V. Czernecki, B. Pillon, J.L. Houeto, J.B. Pochon, R. Levy, B. Dubois, Motivation, reward, and Parkinson's disease: influence of dopatherapy, Neuropsychologia 40 (13) (2002) 2257–2267.
[48] T.W. Robbins, B.J. Everitt, Neurobehavioural mechanisms of reward and motivation, Curr. Opin. Neurobiol. 6 (2) (1996) 228–236.
[49] F. Javoy-Agid, Y. Agid, Is the mesocortical dopaminergic system involved in Parkinson disease? Neurology 30 (12) (1980) 1326–1330.
[50] L. Tremblay, M. Filion, P.J. Bedard, Responses of pallidal neurons to striatal stimulation in monkeys with MPTP-induced parkinsonism, Brain Res. 498 (1) (1989) 17–33.
[51] R. Radakovic, R. Davenport, J.M. Starr, S. Abrahams, Apathy dimensions in Parkinson's disease, Int. J. Geriatr. Psychiatr. 33 (1) (2018) 151–158, https://doi.org/10.1002/gps.4697.
[52] L.B. Zahodne, O. Bernal-Pacheco, D. Bowers, H. Ward, G. Oyama, N. Limotai, et al., Are selective serotonin reuptake inhibitors associated with greater apathy in

Parkinson's disease? J. Neuropsychiatry Clin. Neurosci. 24 (3) (2012) 326–330, https://doi.org/10.1176/appi.neuropsych.11090210.
[53] J.H. Friedman, J.C. Beck, K.L. Chou, G. Clark, C.P. Fagundes, C.G. Goetz, et al., Fatigue in Parkinson's disease: report from a mutidisciplinary symposium, NPJ Parkinson's disease 2 (2016), https://doi.org/10.1038/npjparkd.2015.25.
[54] M. Skorvanek, Z. Gdovinova, J. Rosenberger, R.G. Saeedian, I. Nagyova, J.W. Groothoff, et al., The associations between fatigue, apathy, and depression in Parkinson's disease, Acta Neurol. Scand. 131 (2) (2015) 80–87, https://doi.org/10.1111/ane.12282.
[55] A.F. Leentjens, K. Dujardin, L. Marsh, P. Martinez-Martin, I.H. Richard, S.E. Starkstein, et al., Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations, Mov. Disord. 23 (14) (2008) 2004–2014.
[56] P. Martinez-Martin, C. Rodriguez-Blazquez, M.J. Forjaz, M.M. Kurtis, M. Skorvanek, Measurement of nonmotor symptoms in clinical practice, International Review of Neurobiology vol. 133, Elsevier, 2017, pp. 291–345.
[57] R. Weintraut, K. Karádi, T. Lucza, M. Kovács, A. Makkos, J. Janszky, et al., Lille apathy rating scale and MDS-UPDRS for screening apathy in Parkinson's disease, J. Parkinson's Dis. 6 (1) (2016) 257–265.
[58] R.S. Marin, R.C. Biedrzycki, S. Firinciogullari, Reliability and validity of the apathy evaluation scale, Psychiatr. Res. 38 (2) (1991) 143–162.
[59] P. Robert, S. Clairet, M. Benoit, J. Koutaich, C. Bertogliati, O. Tible, et al., The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment, Int. J. Geriatr. Psychiatr. 17 (12) (2002) 1099–1105.
[60] J.L. Cummings, M. Mega, K. Gray, S. Rosenberg-Thompson, D.A. Carusi, J. Gornbein, The Neuropsychiatric Inventory comprehensive assessment of psychopathology in dementia, Neurology 44 (12) (1994) 2308.